ARTICLE

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HER2 POSITIVE BREAST CANCER IN ELDERLY PATIENTS: TUMOR BIOLOGY AND SPECIFICITIES OF SYSTEMIC TREATMENT

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Summary

Breast cancer is the most common cancer in females and it is primarily disease of ageing with highest incidence in women older than 65 years. There are statistically significant differences in breast cancer histology considering patients age and older patients are usually diagnosed with larger, hormone sensitive tumors. Approximately 15-25% of all women diagnosed with early breast cancer have tumor overexpressing HER2/neu receptor. A golden standard for early and metastatic HER2 positive breast cancer treatment is trastuzumab. Studies in adjuvant setting showed that one year of trastuzumab therapy reduces the risk of death by one-third. Important side effect of trastuzumab treatment is cardiotoxicity, whose precise mechasnisms are not clear yet. The aim of our study was to determine differences in biological characteristics of tumor, treatment options and cardiac side effects in elderly patients with HER2 positive early breast cancer. Research included patients with early, histologically confirmed, HER2 positive breast cancer who underwent prior breast surgery and axillary node dissection. Patients were divided into two groups considering age: group I ≤ 65 years of age and group II > 65 years of age. Patients received adjuvant anthracycline or non-antracycline based chemotherapy followed by one year of trastuzumab monotherapy. Cardiac function was monitored with echocardiography by measuring left ventricle ejection fraction (LVEF) in patients before starting trastuzumab, 3 months and 8 months after trastuzumab was introduced. Incidence of trastuzumab induced cardiac dysfunction showed no significant difference between younger and older patients except in group of older patients with cardiovascular risk who had significantly higher incidence of cardiac dysfunction.

KEY WORDS: *breast cancer, HER2 positive, trastuzumab, cardiac dysfunction*

HER2 POZITIVNI KARCINOM DOJKE U STARIJIH BOLESNICA: BIOLOGIJA TUMORA I SPECIFIČNOSTI SISTEMSKOG LIJEČENJA

Sažetak

Karcinom dojke je najčešći karcinom u žena i primarno je bolest starenja s najvećom incidencijom u žena dobi iznad 65 godina. Postoje statistički značajne razlike u histologiji karcinoma dojke obzirom na dob bolesnice i starije bolesnice obično imaju veći, hormonski ovisan tumor. 15-25% svih žena kojima se dijagnosticira rani karcinom dojke imaju tumor koji pretjerano eksprimira HER2/neu receptor. Zlatni standard za liječenje ranog i uznapredovalog HER2 pozitivnog karcinoma dojke je trastuzumab. Studije u adjuvantnom liječenju su pokazale da jednogodišnje terapija trastuzumabom smanjuje rizik od smrti za jednu trećinu. Važna nuspojava liječenja trastuzumabom je kardiotoksičnost, čiji mehanizmi nastanka još nisu potpuno razjašnjeni.

Cilj našeg istraživanja je bio utvrditi razlike u biološkim karakteristikama tumora, terapijskim opcijama i kardijalnim nuspojavama u starijih bolesnica s ranim HER2 pozitivnim tumorom dojke.

U istraživanje smo uključili bolesnice s ranim, histološki potvrđenim, HER2 pozitivnim karcinomom dojke koje su ranije liječene kiruški, operacijom dojke i odstranjenjem aksilarnih limfnih čvorova. Bolesnice su podijeljene u dvije skupine

obzirom na dob: grupa I – mlađe od 65 godina i grupa II – starije od 65 godina. Bolesnice su primile adjuvantnu kemoterapiju na bazi antraciklina ili protokolom bez antraciklinskog preparata nakon čega je slijedilo liječenje trastuzumabom u monoterapiji kroz godinu dana. Srčana funkcija je praćena uz pomoć ehokardiografije, mjerenjem ejekcijske frakcije lijevog ventrikla prije početka terapije trastuzumabom te 3 i 8 mjeseci nakon početka terapije trastuzumabom.

Incidencija trastuzumabom inducirane kardiotoksičnosti nije pokazala statistički značajnu razliku između mlađih i starijih bolesnica, osim u grupi starijih bolesnica sa kardiovaskularnim rizikom, koje su imale značajno veću incidenciju srčanog popuštanja.

KLJUČNE RIJEČI: *karcinom dojke, HER2 pozitivan, trastuzumab, srčano popuštanje*

INTRODUCTION

Breast cancer is the most common cancer in females and it alone contributes 25% of new cancer cases in the world. Breast cancer is primarily disease of ageingwith an incidence rate (USA) of 82,2 per 100000 in women younger than age 65 years versus 403,8 per 100000 for those age 65 years and older. The average age at diagnosis is 61 years and the average age at death is 68 years (1). In the UK the majority of breast cancers are diagnosed in women over 50 years of age, of which 31% are in patients aged 70 and over (2). In most countries about 40% of breast cancer cases occur in women aged 65 years and older, and the incidence of breast cancer among older women is expected to increase in the future (3). Ageing and severe comorbidities reduce tolerance to treatments which should be considered when choosing the appropriate therapy for elderly patients (3,4).Elderly women are often diagnosed at the late stage due to delayed physician visit. 3% of women in the 50-69 age group are diagnosed at the late stage, 8% of women aged over 70 years have a late stage at diagnosis which diminishes survival rate (5).Croatian demographic statistics show trend of ageing population and the country has one of the highest percentages of population over 65 years. According to Croatian National Cancer Register data there were 2500new cases of breast cancer registered in 2010 and 1100 registered deaths from breast cancer (6).Incidence and mortality grow continuously. Since October 2006 Croatian government started National program for early breast cancer detection *Mamma* which consists of mamography examination every two years for all females aged 50 to 69 years (7).

There are statistically significant differences in breast cancer histology considering patients age and older patients usually have larger hormone sensitive tumor(8).Approximately 15-25% of all women diagnosed with early breast cancer have tumor that overexpresses HER2/neureceptor which is result of exessive amplification of erbB2 gene (9,10). Patients with breast cancer in which HER2 is overexpressed are likely to have poorly differentiated tumors with a high proliferative rate, positive axillary lymph nodes, and decreased expression of estrogen and progesterone receptors. These characteristics are associated with an increased risk of disease recurrence and death (11,12). A golden standard for early and metastatic HER2 positive breast cancer treatment is trastuzumab, recombined humanizedmonoclonal antibody (IgG) with high affinity for the extracellular domain of erbB2 (HER2) transmembrane receptor (11–13). The combination of trastuzumab and a chemotherapeutic agent improves 1-year survival in women with metastatic breast cancer by 16% (14–18). Phase three studies in adjuvant treatment NSABP-B31 (National Surgical Adjuvant Breast end Bowel Project),NCCTG N 9831 (North Central Cancer Treatment Group), HERA (Herceptin Adjuvant trial)and BCIRG 006 (Breast Cancer International Research Group) showed clinical benefit: one year of trastuzumab therapy reduces the risk of death by one-third (10,19–23). Clear clinical benefit of trastuzumab therapy is shown after few years: in the 4-year follow-up of the joint efficacy analysis from NSABP B-31 and NCCTG N 9831, the addition of trastuzumab to chemotherapy resulted in a 48% reduction in DFS events, and 93% of patients who recived trastuzumab were alive 4 years after diagnosis (24). Important side effect of trastuzumab treatment is cardiotoxicity, whose precise mechasnisms are not clear yet(11). HER2 in myocytes plays important role in embryogenesis, contractility and cell death (11,25–28). Binding to HER2 receptor, trastuzumab blocks activity of neuregulin 1β, paracrine mediator that affects

contractility and cell proliferation, which leads to cardiac dysfunction (29–31). Clinical studies showed 6.2% (HERA) to 19% (NSABP-B32) suspension of trastuzumab therapy due to decrease in LVEF (25).

Adjuvant chemotherapy improves survival in women with early breast cancer. Age, comorbidity and life expectancy should be considered when choosing the appropriate adjuvant treatment. Women aged 50–69 years with breast cancer achieve a 20% proportional reduction in the risk for recurrence and an 11% proportional reduction in the risk for death with adjuvant chemotherapy (3). There are limited data on chemotherapy benefit in patients over 70 years of age due to lower percentage of elderly patients included in fewer clinical trials.

The Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis, which included as few as 1,529 patients aged >70 years in comparison with more than 31,000 patients <70 years, found a nonstatistically significant 13% reduction in all-cause mortality among women aged 70 years and older who received adjuvant chemotherapy. Life expectancy represents a central concept in decision making in the elderly patient with breast cancer, because treatment options now available often carry risks and toxicities in older women. Nonlinear relationship between age and life expectancy is crucial in clinical decision making: women aged 65, 75, and 85 years in good health can expect to live, on average, an additional 20, 12, and 6 years, respectively. The choice of adjuvant treatment for elderly patients should be based on the same criteria that are currently used for other age groups (3).

AIM

To determine differences in biological characteristics of tumor, treatment options and cardiac side effects in elderly patients with HER2 positive early breast cancer.

MATERIALS AND METHODS

Research included patients with early, histologically confirmed, HER2 positive breast cancer who underwent prior breast surgery and axillary node dissection. Patients were divided into two groups considering their age: group I –patients under 65 years of age and group II – patients older than 65 years of age. Year of birth, size of tumor, axillary lymph node status, steroid receptor status and HER2 status were determined for all patient.

Patients received adjuvant chemotherapy based on antracyclines –AC (Adriamycin 60mg/m^2 and Cyclophosphamide 600 mg/m^2) for 6 cycles; AC for 4 cycles followed by paclitaxel for 4 cycles (175 mg/m^2) or non-antracycline based chemotherapy - CMF (Cyclophosphamide 600mg/m^2, Methothrexate 40 mg/m^2 and 5-Fluorouracil 600 mg/m^2) for 6 cycles in three weeks intervals. After adjuvant therapy was completed, treatment was continued with trastuzumab every three weeks for one year.

Cardiac function was monitored with echocardiography by measuring left ventricle ejection fraction (LVEF) in patients before starting trastuzumab, 3 months and 8 months after initiation of trastuzumab. Patients who developed cardial dysfunction underwent echocardiography after two weeks and than every two months until LVEF recovered. Cardial dysfunction was defined as drop in LVEF by ≥ 15% of basal value or ≥ 10% of lower normal value (= 50%).

RESULTS

Follow up included 230 patientswith early HER2 positive breast cancer in period from January 1st 2007 until December 31st 2009. Median follow up period was 35 months (16-52 months). Patients were 35 to 77 years old (median 58 years). 190 (82,6%) were younger than 65 years – group I, and 40 (17,4%) were over 65 years – group II.

Biological characteristics of tumor were different regarding patients age: 50% of patients younger than 65 years hada tumor smaller than 2 cm while 75% of patientsover 65 years had a tumor larger than 2 cm. Older patients had statistically higher incidence of larger tumor, over 2 cm (chi^2 test, chi=8.32, df=1, p=0.004) (Table 1., Figure 1). There was no statistically significant difference in axillary lymph node infiltration between groups. 41,6% younger patients vs 42,5% older patients had negative axillary lymph nodes status (N0). One to three axillary lymph nodes were positive (N1) in 23,7% ofyounger vs 20,0% in older patients. Metastases in ≥ 4 axillary lymph nodes

Table 1.

HER2 POSITIVE BREAST CANCER CHARACTERISTICS REGARDING PATIENTS AGE

Characteristics	Age ≤ 65 years (∑N = 190)		Age > 65 years (∑N = 40)	
	N	%	N	%
Tumor size ≤ 2 cm	95	50,0	10	25,0
Tumor size>2 cm	95	50,0	30	75,0
N0	79	41,6	17	42,5
N1	45	23,7	8	20,0
N2 i N3	66	35,7	15	37,5
ER i PR negative	106	56,0	15	37,5
ER i PR positive	84	44,0	25	62,5

(N2,N3) were found in 35,7% of younger vs 37,5% of older patients.There was no statistically significant difference in lymph node (N) involvement between two groups (chi^2 test, chi=0.273, df=2, p=0.872) (Table 1., Figure 2).

Hormone sensitivity of tumor was different regarding patients age: 56% of younger patients had ER/PR negative tumor whereas 62,5% of older patients had ER/PR positive tumor. Younger patients had significantly higher incidence of hormone (ER and PR) negative breast cancer (chi^2 test, chi=15.21, df=1, p<0.001) (Table 1., Figure 3).

Considering the stage of breast cancer: 30% of patients in group I had a stage I disease vs 25% of patients in group II; 30% of patients in group I had a stage II disease vs 45% in group II; 40% of patients in group I had a stage III disease vs 30% in group II. (Table 2., Figure 4.) There was no statistically significant difference in stages between groups (chi^2 test, chi=3.43, df=2, p=0.180).

All the patients received adjuvant therapy after surgical treatment; all the patients in younger group received anthracycline based regimen while 82.5% of older patients received anthracyclines. 17.5% of older patients received non-anthracycline based chemotherapy (CMF) due to increased cardiovascular risk. Significantly larger number of younger patients received anthracycline based chemotherapy (proportion test, p< 0,001). (Figure 5.)

Incidence of cardiac dysfunction was 12,2% and there was no statistical difference between two age groups. Treatment with trastuzumab was continued in 69.5% of younger patients after cardiac therapy and LVEF recovery. None of patients older than 65 years continued trastuzumab treatment due to comorbidity, prolonged cardiac recovery, benefit/risk assessmentor due to patients personal preferences (Table 3).

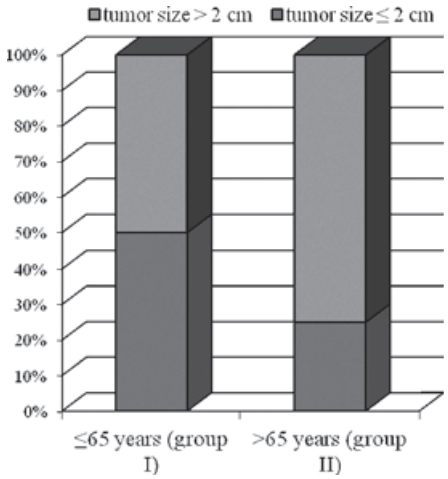

Figure 1. Tumor size regarding patients age

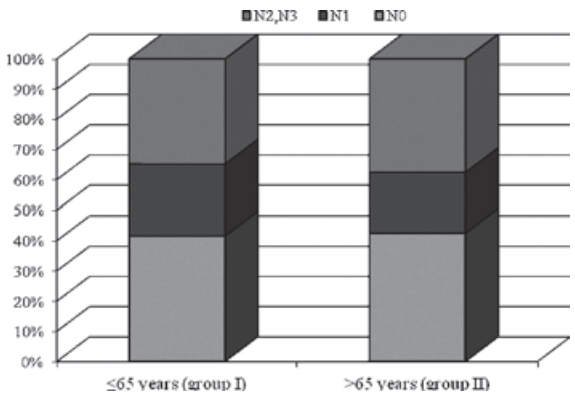

Figure 2. Metastases in axillary lymph nodes

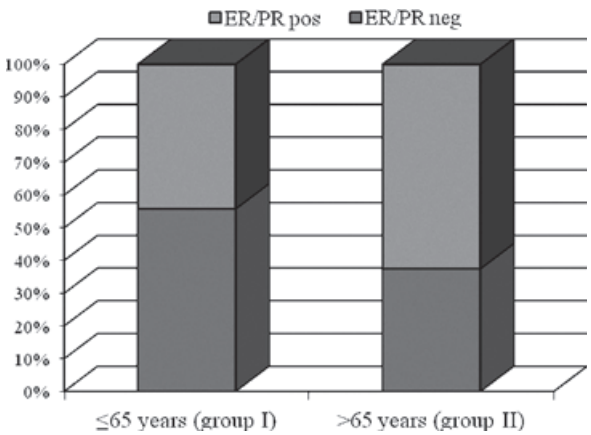

Figure 3. Steroid receptor status regarding patients age

Table 2.

BREAST CANCER STAGE

Stage	Age ≤ 65 years (∑N = 190)		Age > 65 years (∑N = 40)	
	N	%	N	%
I	57	30,0	10	25,0
II A B	 41 16	 21,6 8,4	 9 9	 22,5 22,5
III A B	 53 23	 27,9 12,1	 12 0	 30,0 0

Table 3.

SYMPTOMATIC SYSTOLIC CARDIAC DYSFUNCTION

Age (years)	Trastuzumabom therapy		Cardiac dysfunction		Trastuzumabom continuation	
	N	%	N	%	N	%
≤65 (group I)	190	82,6	23	12,1	16/23	69,5
>65 (group II)	40	17,4	5	12,5	0	0
TOTAL	230	100,0	28	12,2	16 /28	57,0

Table 4.

CARDIOVASCULAR RISK AND CARDIAC DYSFUNCTION

Cardiovascular risk	Cardiac dysfunction			
	YES		NO	
	N	%	N	%
Group I – patients with cardiovascular risk (N= 53)	8	15,1	45	84.9
Group II – patients with cardiovascular risk (N= 20)	6	30,0	14	70,0

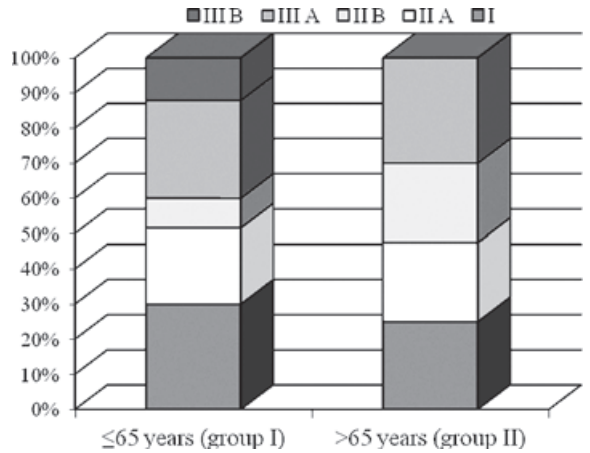

Figure 4. Breast cancer stage regarding patients age

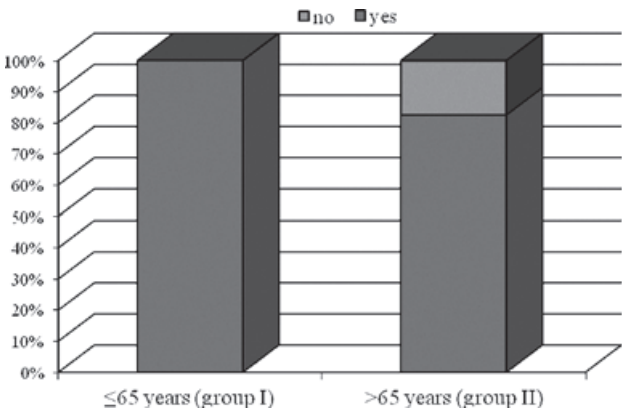

Figure 5. Antracycline based chemotherapy

DISCUSSION

In the last few decades there is a trend of ageing of population in the world which leads to increased incidence of breast cancer among older age groups. There are differences in tumor histological characteristics between younger and older patients whose tumors usually show slower growth, lower aggressiveness and higher hormone sensitivity. Older age is associated to significant comorbidity which affects tolerance to antineoplastic drug and can affect treatment choice (1,4,8).

In our research17% of patients were older than 65 years which leads to conclusion that there is lower incidence of HER2 positive tumors in older age groups, e.g. there is a higher incidence of less aggressive tumors in older age groups.

Despite tumor size in older group (75% of tumors were larger than 2 cm), there was no statistically significant difference in axillary lymph node infiltration or disease stage which also indicates lower tumor aggressiveness. On the other hand, women over 69 year are not included in National program for early breast cancer detection and they usually delay their visit to a doctor, which can explain significant difference in tumor size between groups. 62,5% of tumors in older age were hormone sensitive which is consistent with the literature data (8).

There are differences in applied adjuvant chemotherapy protocols due to significantly higher comorbidity and cardiovascular risk in older women. Younger patients received anthracycline based chemotherapy more frequently (100%) than the older ones (82,5%).

Symptomatic cardiac dysfunction incidence was 12.2%, without statistically significant differ-

ence between groups. Incidence of cardiac dysfunction in patients with cardiovascular risk was 30% in group of older patients compared to 15% in group of younger ones. Similar results, for elderly women with cardiovascular risk who received trastuzumab, were presented by C. Serrano (32). After development of cardiac dysfunction, older patients did not continue trastuzumab treatment due to prolonged and inadequate recovery of cardiac function.

CONCLUSION

There are statistically significant differences in biological characteristics and chemotherapy regimens for HER2 positive early breast cancer in elderly women. Incidence of trastuzumab induced cardiac dysfunction showed no significant difference between younger and older patients except in group of older patients with cardiovascular risk who had significantly higher incidence of cardiac dysfunction.

REFERENCES

1. Muss HB, Busby-Whitehead J. Older women with breast cancer: slow progress,great opportunity, now is the time. J Clin Oncol. 2011;29(35):4608-10.
2. www.ncin.org; Breast Cancer in the Elderly. Accessed on 15.01.2014.
3. Dellapasqua S, Colleoni M, Castiglione M, Goldhirsch A. http://theoncologist.alphamedpress.org/content/12/8/952.full - aff-1New criteria for selecting elderly patients for breast cancer adjuvant treatment studies. Oncologist. 2007;12(8):952-959.
4. Bernardi D, Errante D, Galligioni E, Crivellari D, Bianco A et al. Treatment of breast cancer in older women. Acta Oncol. 2008;47(2):187-198.
5. www.cancerresearchuk.org; Late breast cancer diagnosis in elderly leads to poor survival. British Journal of Cancer, 2011. Accessed on 15.01.2014.
6. www.hzjz.hr; Mihel S,Rodin U. Pobol i uzroci smrti osoba starije životne dobi u Hrvatskoj. Accessed on 15.01.2014.
7. www.hzjz.hr; Registar za rak. Accessed on 15.01.2014.
8. Diab SG, Elledge RM, Clark GM: Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst. 2000;92(7):550-556.
9. Singer CF, Köstler WJ, Hudelist G: Predicting the efficacy of trastuzumab based therapy in breast cancer: current standards and future strategies. Biochim Biophys Acta. 2008;1786(2):105-13.
10. Rayson D, Richer D, Chia S, Jackisch C at al. Antracycline-trastuzumab regimens for HER2/neu-overexpressing breast cancer: current experience and future strategies. Ann Oncol. 2008;19(9):1530-9.
11. Fuller SJ, Sivarajah K, Sugden PH. ErbB receptors, their ligands, and the consequences of their activation and inhibition in the myocardium. J Moll Cell Cardiol. 2008;44(5):831-54.
12. Hortobagyi GN. Trastuzumab in the treatment of breast cancer. N Engl J Med 2005; 353(16):1734-6.
13. Guglin M, Cutro R: Trastuzumab-induced cardiomyopathy. J Card Fail. 2008;14(5):437-44.
14. Feldman AM, Lorell BH. Trastuzumab in the treatment of metastatic breast cancer: anticancer therapy versus cadiotoxicity. Circulation. 2000;102(3):272-4.
15. Jerian S, Keegan P: Cardiotoxicity associated with paclitaxel/trastuzumab combination therapy. J Clin Oncol. 1999;17(5):1647-8.
16. Lunardi G, Vanozzi MO, Bighin C at al. Influence of trastuzumab on epirubicin farmacokinetics in metastatic breast cancer patients. Ann Oncol. 2003;14(8): 1222-6.
17. Keefe DL. Trastuzumab-associated cardiotoxicity. Cancer 2002;95(7):1592-600.
18. Speyer J. Cardiac dysfunction in the trastuzumab clinical experience. J Clin Oncol. 2002;20(5): 1156-57.
19. Hall PS, Cameron DA. Curent perspective-trastuzumab. Eur J Cancer. 2009;45(1):12-8.
20. Suter TA, Procer M, von Velduisen DJ at al. Trastuzumab-associated cardiac adverse effects in the Herceptin adjuvant trial. J Clin Oncol. 2007;25(25):3859-65.
21. Nielsen DL, Andersson M, Kamby C. HER2-targeted therapy in breast cancer. Monoclonal antibodies and tyrosine kinase inhibitors. Cancer Treat Rev. 2009;35 (2):121-36.
22. Belkacemi Y at al. Concurent trastuzumab with adjuvant radiotherapy in HER-2 positive breast cancer patients: acute toxicity analyses from the French multicentric study. Ann Oncol. 2008;19(6): 1110-6.
23. Slamon DJ, Leyland-Jones B at al. Use of chemotherapy plus monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. New Engl J Med. 2001;344(11):783-92.
24. Romond EH ,Jeong JH, Rastogi P et al. Seven year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node –positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2012;30(31):3792-9.
25. Shaffer R,Tyldesley S, Rolles M at al. Acute cardiotoxicity with concurrent trastuzumab and radiotherapy including internal mammary chain nodes: a retrospective single-institutional study. Radiother Oncol. 2009; 90(1):122-6.
26. Pentassuglia L, Graf M, Lane H at al. Inhibition of ErbB2 by receptor tyrosine kinase inhibitors causes

myofibrillar structural damage without cell death in adult rat cardiomyocytes. Exp Cell Res. 2009;315(7): 1302-12.
27. Leyland – Jones B, Gelmon K, Ayoub JP. Pharmacokinetics, safety and efficacy of trastuzumab administered every three weeks in combination with paclitaxel. J Clin Oncol. 2003;21(21):3965-71.
28. de Korte MA, de Vries EGE at al. 111Indium-trastuzumab visualise myocardial human epiermal growt factor receptor 2 expression shortly after antracycline treatment but not during heart failure: a clue to uncover the mechanisms of trastuzumab related cardiotoxicity. Eur J Cancer. 2007;43(14): 2046-51.
29. Suter TM,Cook-Bruns N. Cardiotoxicity associated with trastuzumab(Herceptin) therapy in the treatment of metastatic breast cancer. Breast. 2004;13(3):173-83.
30. Pentassuglia L, Sawyer DB. The role of Neuregulin-1ß/ ErbB signaling in the heart. Exp Cell Res. 2008; 315(4):627-37.
31. Xu Y, Li X, Zhou M. Neuregulin-1/ErbB signaling: a druggable target for treating heart failure. Curr Opin Pharmacol. 2009;9(2):214-9.
32. Serrano C, Cortes J at al. Trastuzumab-related cardiotoxicity in the elderly: a role of cardiovascular risk factors. Ann Oncol. 2012;23(4):897-902.

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